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Intravitreal gas for symptomatic vitreomacular adhesion: a synthesis of the literature

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PURPOSE: Symptomatic vitreomacular adhesion (sVMA) is defined as visual loss secondary to foveal damage from vitreomacular traction (VMT), and includes isolated VMT, impending macular hole, and full-thickness macular hole with persisting vitreous attachment. Management options include pars plana vitrectomy, intravitreal ocriplasmin, intravitreal gas injection or observation. This synthesis of the literature aimed to assess the safety and efficacy of intravitreal gas for sVMA.

METHODS: Articles describing patients with VMT or macular hole treated with intravitreal expansile gas were selected by systematic literature review using MEDLINE, EMBASE, and the Cochrane Database of Controlled Trials (CENTRAL) up to September 2016. The main outcomes at 1 month and final review were logarithm of the minimum angle of resolution (logMAR) visual acuity (VA), anatomical success (absence of both VMT and macular hole, without pars plana vitrectomy), and adverse events. The intended comparator was observation.

RESULTS: Nine of 106 identified articles were eligible and none were randomized controlled trials. The mean VA of 91 eyes improved from 0.55 (6/21) to 0.48 (6/18) at 1 month and 0.35 (6/13) at final review. The mean VA at final review, prior to a vitrectomy, was 0.42 (6/16). Anatomic success was 48% at 1 month and 57% at final review. The reported adverse events comprised retinal detachment in two highly myopic eyes.

CONCLUSION: Intravitreal gas injection can relieve sVMA. Larger controlled studies are needed to determine safety and efficacy relative to observation, ocriplasmin, or vitrectomy.

Key Words: Gas, Macula, Vitreomacular adhesion, Vitreomacular traction, Vitreous

Introduction

Perifoveal vitreous separation may occur as part of normal ageing, or as part of a disease spectrum ranging from vitreomacular traction (VMT) to macular hole (MH). Symptomatic vitreomacular adhesion (sVMA) is defined as visual loss secondary to foveal damage as a result of VMT, and includes isolated VMT, impending MH, and full thickness MH with persisting vitreous attachment (Jackson et al. 2013; Simpson et al. 2012).

Treatment strategies for VMA depend on disease severity. Asymptomatic VMT can be observed, since vitreofoveal separation may occur spontaneously without sequelae. However, persisting VMT may result in foveal damage, thus prompting treatment if symptoms are significant or visual acuity (VA) is reduced (Hikichi et al. 1995; Melberg et al. 1995; Sonmez et al. 2008). For many years, pars plana vitrectomy (PPV) was the standard approach for VMT (Steel & Lotery 2013). More recently, pharmacological vitreolysis with ocriplasmin (Jetrea; Thrombogenics, Leuven, Belgium) has emerged as an alternative that may avoid the need for PPV (Benz et al. 2010; De Smet et al. 2009; Maier et al. 2015; Stalmans et al. 2010; Stalmans et al. 2012; Gandorfer 2008; Jetrea Summary of Product Characteristics 2013; NICE technology appraisal guidance 2013).

Another treatment modality for sVMA is pneumatic displacement with an intravitreal expansile gas bubble, potentially avoiding the need for vitrectomy or enzymatic vitreolysis. The potential advantage of an intravitreal gas injection includes its low cost and ease of adoption. For example, the cost of ocriplasmin and vitrectomy are estimated at $3 950 (jetrea.com/JETRAOrderinginfo.pdf) and $3 147 in the USA, respectively, and £3 000 and £1 634, respectively, in the UK (Gupta et al. 2008; Nicod et al. 2016). The cost of ocriplasmin is magnified by the fact that many cases fail to respond and therefore still need to progress to vitrectomy. Gases such as C_3F_8 and SF_6 cost as little as £1 if taken from large medical gas cylinders, or typically less than £100 from single use canisters licensed for intraocular use. Intravitreal gas is easy to store and administer, and does not require the

capital costs or surgical expertise needed to undertake PPV. In addition, intravitreal gas injection may potentially be a safer procedure compared to the more invasive PPV.

Given these potential advantages of intravitreal gas we undertook a review of the safety and efficacy of intravitreal gas for sVMA, to guide clinical care or future studies. Specifically, we aimed to determine the benefit of intravitreal gas in terms of releasing VMT or closing MHs, the effect on VA, and the risk in terms of intra- and postoperative complications.

Materials and Methods

Eligibility criteria for considering studies for this review

The population was patients with sVMA, namely VMT with or without MH, to include stage 1, 2 and 3 MH. The intervention was a single intravitreal expansile gas injection. The intended control was natural history. The main efficacy outcomes were VA and anatomic success, defined as an absence of VMT or MH without recourse to PPV. Both outcomes were assessed at 1 month and final follow up. Safety outcomes included all reported surgical complications or adverse events attributed to intravitreal gas. The study protocol was registered with the international prospective register of systematic reviews (2015:CRD42015017338, National Institute of Health Research Centre for Reviews and Dissemination, University of York, UK) and conducted in accordance with Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidance (http://www.prisma-statement.org/, accessed 28 May 2015).

There were no restrictions with regards to gender or ethnicity of patients or language of article. In the anticipated absence of any randomized controlled trials and to maximise safety data, prospective, retrospective, controlled and uncontrolled studies, including case reports, were eligible. Inclusion criteria were: studies of VMT or stage 1-3 MHs (Gass 1988); at least 28 days follow up; VA outcomes reported; either MH closure or VMT release rates; reporting results in adults over 18 years of age. We excluded editorials and expert opinions, and articles appearing as abstract only. Eyes with

prior treatment of VMA were excluded, including PPV, intravitreal gas, and pharmacologic vitreolysis. Eyes being treated for myopic macular hole retinal detachment were excluded.

Search methods for identifying studies

PubMed MEDLINE, EMBASE, and Cochrane Database of Controlled Trials (CENTRAL) searches were performed including all articles up to and including September 2016 using Boolean operators with the following keywords (and corresponding MESH headings if they were available): SF6, sulfur hexafluoride, sulphur hexafluoride, C2F6, hexafluoroethane, C3F8, octafluoropropane, perfluoropropane, gas, intravitreal, macular hole, sulphur hexafluoride, vitreomacular adhesion, and vitreomacular traction. An example search is show in Appendix 1.

Study Selection

Abstracts were retrieved from the search and further articles were identified in the reference lists of the retrieved articles. Two clinicians (JN and TJ) independently assessed articles for provisional eligibility based on their abstract. Full-text copies of all possibly relevant manuscripts were obtained, to determine final eligibility. Any discrepancy in eligibility was resolved by consensus following discussion.

Data collection and risk of bias assessment

Two reviewers (JN and TJ) extracted the relevant information into a database, including: 1) overview of the study (aim and key findings); 2) methodological details (study design, study population, inclusion criteria, exclusion criteria, intervention, comparator if available, study period); 3) VA before and after gas; 4) anatomic success after gas; 5) need for vitrectomy; 6) safety outcomes. To compare across studies, VA was converted to logarithm of the minimum angle of resolution (logMAR) units (Jackson et al. 2013).

Data synthesis and analysis

Where necessary, authors were contacted to obtain unpublished raw data. Two-sided, paired t-tests were used to compare mean VA before and after interventions. Safety was assessed by adverse events (AEs) and serious adverse events (SAEs) reported. Safety data were pooled across all studies, using individual data where available or study means otherwise. Sub-group analysis was performed for those with diagnoses of MH or VMT.

Results

Of 106 articles, 106 abstracts were assessed as potentially eligible, from which nine articles were deemed eligible after full text review. A total of 91 eyes from 90 patients with sVMA were included from one non-randomized controlled study, seven uncontrolled studies and two individual case reports (Table 1) (Chan et al. 1995; Costa et al. 2001; Chen et al. 2012; Jorge et al. 2006; Mori et al. 2007; Gupta & McHugh 2011; Rodrigues et al. 2013; Day et al. 2016; Yu et al. 2016). Additional, anonymous participant-level VA data were obtained from one study author as this information was not available in his report, in accordance with PRISMA guidance (Rodrigues et al. 2013). A risk of bias tool was not used as the literature search found no eligible randomised controlled trials.

(Table 1 Position)

There were 24 males and 59 females, with a mean age of 67.3 years (range 36 to 91, n = 85). Gender and age data were missing from one study of six eyes and the gender of a patient was not stated in one case report. There were 44 eyes (44 patients) with a baseline diagnosis of VMT, including 14 with stage 1 MH. Stage 2 MH was present in 45 eyes (45 patients), and stage 3 MH in 2 eyes (2 patients). One patient underwent bilateral treatment for a stage 3 MH in the right eye and a stage 2 MH in the left eye. Perfluoropropane gas was used in 62 eyes, with the volume injected varying from 0.2ml to 0.5ml. Sulphur hexafluoride 0.5 ml was used in the other 29 eyes. Post-operative posturing techniques were not consistent between studies, varying from 14 days of face down posturing to no posturing. A PPV was performed in 31 of 91 eyes (34%) for varying reasons: persisting MH despite

VMT release with gas in 14 eyes (45%), persisting VMT and MH despite gas injection in eleven eyes (36%), retinal detachment in two eyes (7%), new MH following successful VMT release with gas in two eyes (7%), persisting isolated VMT in one eye (3%) and vitreous haemorrhage secondary to proliferative diabetic retinopathy in one eye (3%).

At 1 month following gas injection, 44 of 91 eyes (48%) had anatomic success, defined as no VMT or MH and without recourse to PPV. At a mean final follow up period of 14.5 months (range: 1 to 48 months), anatomic success was achieved in 52 eyes (57%). Twenty six eyes underwent PPV specifically for failure of gas, 14 for persisting MH, 11 for persisting combined VMT/MH, 1 for persisting isolated VMT, and all responded with anatomic success.

The mean pre-intervention logMAR VA was 0.55 (n = 91; range: 0 to 2.00; Snellen equivalent 6/21). In the 62 eyes (68%) with VA documented at 1 month the mean VA improved from 0.57 logMAR by 0.09 units to 0.48 logMAR (range: 0 to 2.00; 6/18; p=0.036). No eyes had undergone PPV by month 1. Mean VA at final follow up was 0.35 logMAR (n = 88; range: -0.09 to 2.00; 6/13), which was significantly better than baseline (p<0.001)(Table 2). A post hoc analysis of the final VA outcome prior to any PPV revealed a VA of 0.42 logMAR (n=78; 6/16), significantly better than baseline (p=0.001). Three patients did not have a post-gas VA documented.

(Table 2 position)

In the 30 eyes (33%) with a baseline diagnosis of isolated VMT, the mean VA was 0.55 logMAR (range: 0.1 to 2.00; 6/21) at baseline and remained unchanged at 0.55 (range: 0.00 to 2.00; 6/21) at month 1 (n = 22; p=0.226), before subsequently improving to 0.49 (range: 0.00 to 2.00; 6/19) at a mean follow up of 7.7 months (n=28; p = 0.096) (Figure 1). Anatomic success was achieved in fourteen eyes (47%) at month 1 and eighteen eyes (60%) at final follow up (Figure 2). Eight of 30 (27%) eyes with VMT underwent PPV, all after month 1. The indication in one case was vitreous haemorrhage secondary to proliferative diabetic retinopathy in which the initial gas injection had

previously resulted in a complete posterior vitreous detachment (PVD) at month 1. In two eyes, PPV was performed for a full-thickness MH following earlier successful VMT release with gas. The other five PPVs were carried out to treat persistent VMT despite intravitreal gas injection.

A stage 1 MH was present at baseline in 14 eyes. In these eyes, VA improved from 0.31 logMAR (range: 0.18 to 0.48; 6/12) to 0.23 (range: 0.00 to 1.00; 6/10) at month 1 (p=0.338), and significantly to 0.18 (range: 0.00 to 0.30; 6/9) at a mean final follow up of 12.9 months (p=0.015) (Figure 1). Anatomic success occurred in 10 of 14 eyes (71%) at 1 month post-gas, and 13 of 14 eyes (93%) at final follow up (Figure 2).

The distinction between stage 1 (impending) MH and advanced VMT relies on the investigator's judgement and did not appear to be standardised in the literature. Further, impending macular hole is often now grouped together with VMT. We therefore undertook a post hoc analysis combining VMT and stage 1 MH. In this group, VA improved from 0.45 logMAR (range: 0.00 to 2.00; 6/17) to 0.43 (range: 0.00 to 2.00; 6/16) at month 1 (p=0.382), and then improved significantly, relative to baseline, to 0.39 (range: 0.00 to 2.00; 6/15) at a mean follow up of 9.4 months (p=0.019). Anatomic success occurred in 24 of 37 eyes (65%) at 1 month, and 31 of 37 eyes (84%) at final follow up.

There were 45 eyes treated with intravitreal gas for a stage 2 MH, with a mean baseline VA of 0.60 (range: 0.00 to 1.52; 6/24). In the 24 eyes with month 1 VA data, the mean logMAR improved to 0.54 (range: 0.10 to 2.00; n = 24; 6/21). At final follow up (mean = 17.9 months), mean VA significantly improved to 0.28 logMAR (range: -0.09 to 1.00; 6/11) compared to baseline (p<0.001)(Figure 1). Anatomic success occurred in 20 of 45 eyes (44%) at month 1, and 21 of 45 eyes (47%) at final follow up (Figure 2). A PPV was undertaken in 22 eyes. In 20, the indication was failure of MH closure with gas (although 17/20 had resulted in PVD), and all PPVs were successful in closing the MH. The other 2 PPVs were performed successfully to treat retinal detachment.

Two intravitreal gas procedures were performed for stage 3 MH, but neither was successful anatomically either at month 1 or by a final mean follow up of 33 months.

The diameter of MH was only documented in one study of 20 stage 2 MH (Mori et al. 2007). Successful release of vitreous traction and closure of MH at both month 1 and at an average final follow up of 20 months in patients with a MH diameter <250μm was 78% (7/9). Those with larger holes (>250μm) had successful anatomical resolution in 27% of cases (3/11) at 1 month. All those with failed anatomical resolution at one month underwent PPV which resulted in successful MH closure.

Adverse events included two retinal detachments. Both occurred in myopic eyes (-5.75D and -8.50D) with stage 2 MH. In two patients with VMT at baseline, intravitreal gas resulted in PVD at 1 month and development of a full-thickness MH which was successfully closed with PPV. One eye with an impending MH developed a full thickness MH 10 months after failed gas injection, and was successfully closed with PPV. Two eyes with stage 1 MH were diagnosed with macular pseudohole at month 13. There was one patient who was diagnosed with a retinal tear at 1 month following gas, and underwent successful laser retinopexy. No other adverse events were reported.

Discussion

We undertook a review to evaluate the safety and efficacy of intravitreal gas as a treatment for sVMA. We found a lack of high quality evidence. A series of uncontrolled, before/after studies found that 57% of eyes had anatomic success following intravitreal gas, defined as an absence of VMT and MH, without recourse to PPV. There was also a VA gain of 0.13 logMAR units (approximately 1 Snellen line), without the need for PPV. This modest gain in VA may not fully capture the potential symptomatic benefit achieved in this patient group, given that metamorphopsia may be at least as important as VA. The good presenting VA may also impose a ceiling on any VA improvement that can be detected following gas injection. Studies of ocriplasmin and PPV for symptomatic VMA also show

213 modest VA gains, although the visual improvements are often better in the MH subset, compared to
214 those with isolated VMT (Jackson et al. 2013; Stalmans et al. 2012). We also found better VA gains in
215 those with a baseline diagnosis of MH compared to isolated VMT when treated with gas.

216 Our literature search found one study of 20 eyes of 17 patients with VMT that underwent an 0.2ml
217 intravitreal injection of either SF_6 or $C2F_6$ (Claus et al. 2016). This was a retrospective case series
218 which reported an 85% (17/20) overall release of VMT, favourable visual acuity outcomes and no
219 major safety concerns. However, we excluded this study from our analysis because there was
220 insufficient information regarding when VMT release occurred and when post-operative visual
221 acuities were measured (Claus et al. 2016).

222 The management of symptomatic VMA does not currently have a gold standard, with options
223 including observation, intravitreal gas, ocriplasmin, and PPV. Observation of VMT may lead to
224 spontaneous separation in 17-34% of eyes, but conversely some may progress to MH, and prolonged
225 disease may result in loss of vision (Zhang et al. 2015; Almeida et al. 2015).

226 A combined analysis of two randomized controlled trials of ocriplasmin reported that 26.5% of eyes
227 responded within 1 month, with no further response after this time point. Despite using a somewhat
228 stricter definition of success (absence of both VMT and MH, not just an absence of VMT) the rate of
229 release in our review of intravitreal gas appears higher, at 48.4% by month 1 (and 57.1% at final
230 review). However, without direct comparison this conclusion needs to be interpreted with
231 considerable caution, as the difference could reflect patient selection, chance, publication bias, and
232 differences in OCT interpretation, amongst other reasons.

233 In terms of safety, there were three cases of impending MH that progressed to full-thickness MH. In
234 two cases, the gas injection resulted in PVD and full-thickness MH at one month, but the other
235 occurred 10 months after gas injection so causation is unclear. A retinal tear occurred in one case, at
236 month 1 following gas injection, which was successfully treated with laser retinopexy. Most of the

studies did not comment whether the patients were phakic or pseudophakic at baseline. Excluding cases undergoing PPV, two eyes were noted to have progression of nuclear sclerosis but neither required cataract surgery. The most clinically important AEs were two cases of retinal detachment in myopic patients (2%). This suggests that myopic eyes may be best excluded from future studies of intravitreal gas for symptomatic VMA. By extension it may also be reasonable to exclude other risk factors for retinal detachment, such as lattice degeneration or treated retinal breaks, although the risk in these patients in assumed rather than proven. The small number of eyes treated means it is not possible to quantify the overall clinical impact of retinal detachment, however, any such risks needs to be balanced against the risk of PPV or ocriplasmin. A recent literature review of PPV undertaken for VMT found a retinal detachment rate of 4.6% (Jackson et al. 2013). The retinal detachment rate in the pivotal studies of ocriplasmin was 0.4%, vs 1.6% in the placebo group (p=0.16), although several cases of retinal detachment following ocriplasmin have now been published and the true rate of RRD after ocriplasmn with longer follow up may be higher than in the phase 3 trials (Haller et al. 2015; Madi et al. 2016).

The majority of adverse events associated with ocriplasmin have been considered mild, non-serious and transient such as vitreous floaters, eye pain, photopsia and reduced VA (Kaiser et al. 2015). However, concerns remain about dyschromatopsia, ERG changes and severe loss of vision, and there have been isolated case reports of ellipsoid zone changes on OCT and RPE-photoreceptor adhesion release potentially due to the enzymatic activity of the drug (Quezada Ruiz et al. 2015; Hager et al. 2015; Neffendorf et al. 2016; Abraham et al. 2016; Johnson MW et al. 2015).

Only one study reported MH diameter and found a higher success rate of stage 2 MH closure in small diameter holes (<250μm) as opposed to those larger than 250μm (78% vs 27%). This greater efficacy with smaller diameter is consistent with a sub-group analysis of the data from the pivotal ocriplasmin trial (Haller et al. 2015; Jackson et al. 2016). The influence of ERM on anatomic success is hard to determine as most studies excluded ERM, with only four cases included across all studies

(Chan et al. 1995; Day et al. 2016). Rodrigues et al reported that high reflectivity of the inner retinal surface, a possible precursor of ERM, was associated with a lower rate of VMT release (Rodrigues et al. 2013), which is also consistent with the sub-group analysis of the pivotal ocriplasmin trial (Haller et al. 2015; Jackson et al. 2016). It has been shown that phakic patients have a higher likelihood of successful sVMA release following ocriplasmin injection than pseudophakic patients (Haller et al. 2015; Jackson et al. 2016; Feng et al. 2017). In our analysis, only 2 of 9 articles documented whether patients were phakic or pseudophakic at baseline and therefore due to missing data, we did not perform a subgroup analysis to further investigate whether this trend is also seen with intravitreal gas.

A strength of our study is that we have pooled data in a standardised method with predefined outcome measures. However, there are several important weakness. Most importantly the number of patients is low, and only one of the studies had a control group (and in that in turn was not randomised). Accordingly, many studies may be subject to bias. Furthermore, diagnostic criteria varied across studies, as did the type and volume of gas injected and the posturing regimen. Our findings may underestimate VMT release in non-diabetic patients as our group contained 8% (7/91) diabetics, who might be expected to have firmer VMA. In addition, some studies did not report the duration of disease prior to treatment, and others had significant variability in duration (1-7 months). One study was conducted in the pre-OCT era, however, it provided relatively rigorous assessment of VMA including B-scan ultrasonography (Chan et al. 1995). It is also not clear which gas offers the best efficacy.

In conclusion, our synthesis of the literature suggests that there is insufficient evidence to conclude on the safety and efficacy of an intravitreal expansile gas injection for the treatment of sVMA. The limited results available do however appear to justify further research, most helpfully as a comparative study versus other management options such as observation, ocriplasmin, or vitrectomy. Diagnostic inclusion criteria can be defined using recognized photographic standards or

agreed classification systems (Duker et al. 2013; Steel et al. 2016), and outcome measures could be expanded to include cataract progression, validated quality of life questionnaires and assessment of metamorphopsia (Tanner & Williamson 2000; Ugarte et al. 2013; Khadka et al. 2013; Nomoto et al. 2013). An economic evaluation comparing different treatments of symptomatic VMA also appears warranted, given the potential cost advantage of intravitreal gas.

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Figure Legends

Figure 1: Visual acuity

The graph shows the mean logarithm of the minimum angle of resolution visual acuity at baseline, 1 month after intravitreal gas injection, and at final follow up prior to vitrectomy (if carried out). logMAR, logarithm of the minimum angle of resolution; MH, macular hole; VA, visual acuity; VMT, vitreomacular traction.

Figure 2: Anatomic success

The chart shows anatomic success, over time, of intravitreal gas injection for each subset of symptomatic vitreomacular adhesion. Anatomic success was defined as an absence of vitreomacular traction and macular hole, without recourse to vitrectomy. MH, macular hole; VMT; vitreomacular traction.

Appendix 1: Search strategy on MEDLINE

1	1	vitreomacular traction
2	2	vitreomacular adhesion
3	3	macular hole
4	4	or/1-3
5	5	perfluoropropane
6	6	C3F8
7	7	Octafluoropropane
8	8	Sulphur hexafluoride
9	9	Sulfur hexafluoride
10	10	SF6
11	11	Hexafluoroethane
12	12	C2F6
13	13	Gas
14	14	or/5-13
15	15	Intravitreal
16	16	4 and 14 and 15